SENSITIZATION (IgE ANTIBODY) TO FOOD ALLERGENS IN WHEEZING INFANTS AND CHILDREN

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ABBREVIATIONS:

- ab, antibody
- AD, atopic dermatitis
- CI, confidence interval
- DBPC, double-blind placebo-controlled
- GM, geometric mean
- RAST, radioallergosorbent test
- RSV, respiratory syncytial virus

ABSTRACT

Objective: To assess the prevalence of sensitization to common food allergens in a non-selected population of infants and children treated for wheezing in a pediatric emergency room.

Design: Case control study of actively wheezing children who were compared to children without respiratory tract symptoms as well as to children with atopic dermatitis (AD).

Settings: The Pediatric Emergency Room and the Dermatology Clinic at the University of Virginia.

Patients: Convenience sample of 97 wheezing children (2 months to 16 years), 66 control patients (6 months to 16 years), and 60 children with moderate to severe AD (6 months-13 years).

Measurements and Results: Sensitization (IgE ab) to egg, milk, soy, and peanut allergens were measured in sera from patients by RAST. Positive tests were not common in children seen for wheezing in the emergency room under age 2. The prevalence of positive RASTs increased to 24% in wheezing children ages 2 to 4 and to 31% in children after age 4. After the age of two, both the prevalence as well as titers of serum IgE ab to the food allergens in wheezing patients were similar to controls, but were markedly decreased compared to IgE ab responses in sera from AD patients. However, among children ages 2 to 4, RAST tests for sensitization to food allergens and common inhalant allergens were positive in a similar percentage of wheezing patients (24% and 29%, respectively). In addition, one-third of the patients in this age group had IgE ab responses

to foods alone. After age 4, however, most wheezing children with positive RASTs (85%) had IgE ab to inhaled allergens.

Conclusion: Children treated for wheezing in the emergency room had a low prevalence of food sensitization and other atopic markers prior to age 2. After age 2, the prevalence of IgE ab to foods increased as did other findings characteristic of atopy and asthma. Between ages 2 to 4, combining tests for IgE ab to common food and inhalant allergens may enhance efforts to identify wheezing patients who are atopic and who are candidates for allergen avoidance measures. After age 4, most wheezing children with IgE ab were sensitized to inhaled allergens and the data for IgE ab to food allergens suggest that evaluations for food hypersensitivity should be more selective in these children.

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INTRODUCTION

Most studies designed to elucidate the relationship between allergy and asthma in children have focused on the role of inhalant allergens. Between 60-85% of school-aged children with asthma are reported to be sensitized to common aeroallergens (1,2) and environmental controls to reduce exposure to these allergens (e.g. to dust mite) can lead to a significant reduction in bronchial hyperreactivity and symptoms (3-5). In contrast, the importance of immediate hypersensitivity to food allergens among children with asthma is not as well defined. Using tests for sensitization combined with DBPC food challenges, several studies have demonstrated that foods can cause infantile and childhood wheezing in selected patients (6-11). However, based on food challenge studies, it does not appear that food allergens are frequently involved in provoking symptoms of asthma (12).

Other studies of food hypersensitivity during childhood have shown that the development of IgE ab to food allergens begins early in life. In prospective studies, up to 30% of children born to allergic parents were found to be sensitized to common food allergens by a year of age (13-15). In the same studies, however, the development of IgE ab to inhaled allergens was delayed and not often detected by skin test or RAST before age two. Among infants who develop IgE ab to foods, the most frequent clinical manifestation of food hypersensitivity is atopic dermatitis (AD). Several reports have shown that these children have an increased risk for developing respiratory allergies, including asthma, later in childhood (16-18). In addition, other studies suggest that a positive skin test for food

atopic at an early age and have prognostic value as an indicator for the development of allergic respiratory disease (16,19,20). As yet, however, the prevalence of sensitization to common food allergens in infants and children who present with wheezing has never been examined. Previously, in a study of children treated for acute attacks of wheezing in an emergency room, we reported that the prevalence of IgE ab to inhaled allergens was low in those who presented prior to age two (21). After age two, sensitization to these allergens became increasingly common and was significantly increased compared to controls after the age of four. The purpose of the present study was to assess the prevalence of IgE ab to common food allergens by RAST in the same non-selected population of wheezing infants and children.

METHODS

Study Population:

Children in this study included 97 patients who presented to the University of Virginia Pediatric Emergency Room and were given a diagnosis of bronchiolitis or asthma. The age range of these children was from 2 months to 16 years and most (92%) were enrolled during the months of September through June. Wheezing was confirmed by auscultation, and each patient required treatment with at least a beta-2 agonist. Exclusion criteria included a history suggestive of bronchopulmonary dysplasia or recent use of systemic steroids. Sixty-six control patients ranging in age from 6 months to 16 years were also enrolled. These children were enrolled if they had no respiratory tract symptoms and no previous history of wheezing. Sera were also available from 60 children (age 6 months to 13 years) who were seen in the University of Virginia Immunodermatology Clinic for AD.

These children had moderate to severe AD using criteria set forth by Hanifin and Rajka (22). Their sera were included in this analysis because AD is a common clinical manifestation of food hypersensitivity during childhood.

Historical information was obtained from family members with particular attention to each patient's birth and allergic history as well as the presence of allergic disease in other members of the immediate family (parents and siblings). This study was approved by the human investigation committee at the University of Virginia and informed written consent was obtained from patients or their parents. Additional demographic characteristics of the study groups are presented in Table 1.

Immunoassays:

Sera from enrolled patients were stored at -20° C and subsequently analyzed for IgE ab to egg white, cow's milk, soy and peanut allergens. These allergens were selected after reviewing skin test data from 63 food-sensitized children seen in the pediatric allergy clinic at the University of Virginia. These patients had a positive skin test (i.e. a wheal 3 mm greater than a saline control) to one or more food allergens, and 92% of them could be detected using a screen inclusive of these four allergens. This finding is also consistent with other reports (23).

IgE ab was measured by RAST using cyanogen-bromide activated filter paper discs coated with allergen using methods previously described (24). The starting materials for the preparation of allergen extracts included crude dried egg white (Sigma #A5253), β-lactoglobulin A and B (Sigma #L2506), isolated soy proteins (Ralston-Purina Lot #C6C-E0070) and peanut proteins (defatted Florunner variety). Concentrated extracts of each

allergen were made by suspension of the crude material in bicarbonate coating buffer (0.1M $NaHCO_3$ + 0.5M NaCl, ph 8.0) followed by an overnight incubation on a rotator. After centrifugation, extracts were dialyzed extensively in coating buffer and then recentrifuged. The protein concentration, determined by Bradford assay, was > 3.0 mg/ml for each extract (25). To optimize the amount of allergen coated to discs, serial four-fold dilutions of each extract were coupled to RAST discs followed by incubation, washing and blocking as previously described (24). Discs were then incubated with pooled sera from at least 5 patients who had strongly positive skin tests for the same allergen being tested. The concentration of each extract showing maximal binding of IgE ab to the discs was chosen for coating discs in this study.

To test sera from patients, discs coated with allergen were incubated with sera diluted 1:4 in duplicate. In order to conserve sera from pediatric patients a modified micro-RAST procedure, utilizing 17 μl of serum per test, was used (26). Bound IgE ab was detected using radiolabelled goat anti-human IgE. Sera from 8-10 patients who were skin test negative served as controls in each assay. Two positive control sera were also included as were two sera with elevated total IgE levels which did not contain specific IgE ab to the allergen tested.

For egg, milk and peanut RAST tests, sera with IgE ab binding $\geq$ 3 standard deviations above the mean counts per minute of 10 negative controls were considered to be positive. For soy, IgE ab binding $\geq$ 4 standard deviations above the mean was read as positive. These criteria were established after comparing RAST and skin test data from 52 food-sensitized clinic patients. The concordance between the RAST assays using these

food-sensitized clinic patients. The concordance between the RAST assays using these criteria and prick skin tests was 89%, 82%, 86%, and 85% for egg, milk, soy, and peanut, respectively. There were more false negative than false positive RAST responses. The total concordance between these tests (86%) is high and is in agreement with reports from others (27).

Using this food screen, sera with IgE ab to one or more of the allergens tested were considered food RAST positive. To judge titers of specific IgE ab, a control curve was developed for each allergen utilizing serial two-fold dilutions of sera pooled from five patients with positive skin tests to the allergen tested. Because the quantity of allergen coated to discs for egg, milk, soy, and peanut was not likely to be identical, and because the slope of the control curves for these four allergens were also not the same, titers of IgE ab in sera were expressed as a percent of the maximum counts bound at the top of each control curve for each allergen. Measurements of total serum IgE were performed by ELISA as described previously (28). To minimize non-specific IgE binding, sera from patients with high total IgE were diluted to obtain a total IgE level of < 1000 IU/ml.

Statistical Analysis:

To compare differences between the percentage of wheezing, control, and AD patients who were food RAST positive, Chi-square analyses and Fisher's exact test were used. Continuous responses were compared using two sample t-tests. All hypothesis testing was based on two-sided tests of significance (29).

RESULTS

Among 27 patients who presented with acute wheezing prior to age two, only one had specific IgE ab to one or more food allergens (Fig. 1). This child was 22 months old and was RAST positive to egg. Previously, this patient was also shown to have IgE ab to dust mite (21). None of the control patients in this age group had IgE ab to the food allergens tested. Among the 21 wheezing children from 2 to 4 years of age, sera from 24% were RAST positive compared to 14% of sera from controls. In children over 4 years, the percentage of RAST positive sera did not increase significantly (31%) and was not significantly different from controls (Fig. 1). The increase in specific IgE ab after age 2 was also reflected in the results for individual food allergens (Fig. 2A).

Compared to the findings in wheezing and control patients, a high percentage of sera (84%) from AD patients under age 2 contained IgE ab to one or more food allergens. The prevalence of food-specific IgE antibody in the 2-4 and over 4 age groups with AD was 75% and 63%, respectively. In each age group, the percentage of sera which were food RAST positive was significantly greater in AD patients than in wheezing or control patients ($p < 0.001$ and $p < 0.001$, respectively). This increase was apparent for all four allergens tested (Fig. 2C). Among wheezing and control patients under age 4 as well as AD patients under age 2, sensitization to egg was detected more often than sensitization to milk, soy, or peanut.

The geometric mean (GM) of food-specific IgE ab in each serum was expressed as a percent of the maximal binding of radiolabelled goat anti-human IgE ab at the top of each allergen control curve (Fig. 3). For wheezing patients the GM's of IgE ab to egg, milk, soy, and peanut from those who were RAST positive were 13%, 12%, 20%, and 5%, respectively.

The GM values for egg, soy, and peanut were similar to controls (13%, 25%, and 9%, respectively). In contrast, the GM of titers to these allergens, except for milk, were significantly lower than the mean titers from RAST positive AD patients (37% for egg, 13% for milk, 44% for soy, and 16% for peanut, $p < 0.001$ for egg, soy, and peanut).

Measurements of IgE ab to inhalant allergens in sera from the wheezing patients were reported in a previous study (21). Shown in Table 2 is an analysis of RAST responses in patients from whom sera were available for measurements of IgE ab to both food and inhalant allergens. Most wheezing children under age two (93%) lacked IgE ab to either food or inhalant allergens. However, between 2 to 4 years of age, 43% of these children were sensitized to food and/or inhalant allergens. In this group, the percentage of patients with IgE ab to food allergens and inhalant allergens was approximately the same (24% and 29%, respectively), and one-third of the RAST positive patients were sensitized to foods only. After age 4, a marked increase in the percentage of patients sensitized to aeroallergens (59%) was observed. This accounted for 85% of the RAST positive patients in this age group. The GM of total serum IgE in children over four who had IgE ab responses only to inhaled allergens was 225 IU/ml. This was significantly higher than the GM of total IgE in sera from children who only had IgE responses to food allergens (GM = 55 IU/ml, $p < 0.001$).

DISCUSSION

Among children who presented to the emergency room with wheezing prior to age two, the prevalence of serum IgE ab to food allergens in this study was low. Only one patient, who was almost two years old, had a positive RAST test to food allergen (i.e. to egg) and was also previously shown to have IgE ab to dust mite (21). Most of these children presented with their initial attack of wheezing and were diagnosed with bronchiolitis. In addition, viral respiratory pathogens, particularly RSV, were cultured from nasal secretions from 70% of these patients (21). RAST tests were used to measure IgE ab in this study because skin tests are not indicated for actively wheezing patients. Although RAST tests can be less sensitive than skin tests, it is likely that the low prevalence of serum IgE ab to food allergens reflects a low rate of atopy among this group of infants who also had low total IgE levels, a low prevalence of IgE ab to inhaled allergens and only one child (the patient with IgE ab to mite and egg) had nasal eosinophilia. In addition, the concordance between the food RASTs used for this study and skin tests with the corresponding allergens in clinic patients was high (86% overall).

Consistent with other studies of food hypersensitivity in children with eczema, a high prevalence of food sensitization was detected in sera from the children with moderate to severe AD who were under age two (30,31). This finding is pertinent to other reports which, on one hand, suggest that infants with bronchiolitis may have an allergic predisposition or have an increased risk for subsequent wheezing, but which, on the other hand, include a substantial number of children with eczema (32,33). We have also compared our results from the emergency room patients with observations of infants who

are referred for wheezing to the pediatric allergy clinic. In clinic, patients are almost always referred because they have a history of repeated or persistent episodes of wheezing, an immediate family history for allergy or asthma, and/or eczema. Like infants from the emergency room, these children also have a low prevalence of sensitization to aeroallergens prior to age two; however, up to a third may have positive prick skin test responses to food allergens. Because of their sensitization to food allergens, these children may have a greater risk for developing IgE ab to inhaled allergens and respiratory symptoms later in childhood (16-18). In contrast, it is not clear that children who present with bronchiolitis, but without AD or IgE ab to environmental antigens, have an increased risk for developing asthma as they grow older (34).

Food sensitization increased among wheezing children after age 2 in this study. Many of the children ages 2 to 4 (77%) had a history of prior wheezing and, although four (18%) had a history of eczema, none had active skin disease. In this age group, the RAST tests for foods were positive in approximately the same percentage of wheezing patients as RAST tests for inhalants. Furthermore, 1/3 of the RAST positive children were identified by food tests alone. Thus, combining tests for IgE ab to common food and inhalant allergens in this age group may enhance efforts to identify wheezing patients who are atopic and who, in turn, may benefit from allergen avoidance measures in managing their symptoms.

After age 4, a marked increase in the percentage of patients with IgE ab to inhalant allergens was noted relative to foods. In fact, the majority of patients with serum IgE ab (85%) had positive RAST tests for inhalants. In addition, the prevalence of sensitization and titers of IgE ab to individual food allergens in this group (only 10% of whom had a

history of AD) did not differ significantly from controls, but were much lower than from AD patients. In other studies, bronchospasm has been reported following DBPC food challenges in selected patients with asthma, more often in those with AD or a history of symptoms consistent with food allergy (6-11). These studies, together with our results, indicate that the evaluation of food hypersensitivity in older children with asthma should be more selective and include those who have a history of AD or food-induced wheezing. In addition, when tests for food sensitization are positive, further evaluation (e.g. food challenge studies) is needed to judge the clinical relevance of a positive test (12).

In conclusion, although a number of studies have demonstrated that sensitization to inhaled allergens is common in children with asthma, the relationship between childhood wheezing and sensitization to food allergens is not as clear. Sensitization to food allergens begins early in life and is strongly associated with symptoms of AD in infancy. It has also been reported that young children who are sensitized to food allergens, including those with or without AD, have an increased risk for developing allergic respiratory symptoms including asthma. Thus, it would be useful to know whether tests for foods could identify wheezing infants who are atopic, but who had not yet developed IgE ab to aeroallergens. In this study, however, IgE ab to food allergens was not a common finding in infants treated for wheezing in an emergency room. These children, in contrast to those infants referred to an allergy clinic for recurrent or persistent wheezing, also had a low prevalence of other risk factors for atopy. Among wheezing children ages 2 to 4, results from the emergency room revealed that tests for IgE ab to common food allergens may enhance efforts to identify atopic children who would not be identified by tests for inhaled allergens alone. After age

4, most wheezing children with serum IgE ab had positive tests for inhalants and, in this age group, the data would support recommendations to test for IgE ab to food allergens in wheezing children more selectively, particularly in those who have a history of AD or food intolerance.

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Legends for Figures:

Figure 1:

The percentage of sera from wheezing patients (black bars) and controls (hatched bars) with IgE ab to food allergens are compared. In each serum, IgE ab was measured by RAST to egg, milk, soy, and peanut allergens. Sera testing positive to one or more of these allergens were defined as food RAST positive.

Figure 2:

The percentage of sera with IgE ab to egg (black bars), milk (slanted hatched bars), soy (open bars) and peanut (vertical hatched bars) are shown according to age for wheezing (A), control (B), and AD patients (C). The sample size of each age group is indicated in parentheses.

Figure 3:

Titers of IgE ab to egg (E), milk (M), soy (S), and peanut (P) were measured by RAST. The results in sera from AD, wheezing, and control patients are compared for children age 2 years and older. Titers are expressed as a percent of maximal counts bound of radiolabelled goat anti-human IgE ab at the top of a control curve established for each allergen. Solid circles (●) represent sera which were positive for IgE ab to each allergen. Numbers below the solid lines followed by an open triangle (△) represent the number of sera which tested negative.

Table 1. Patient Characteristics:

	CHILDREN <2			CHILDREN ≥2		
	Wheezing Patients	Controls	AD Patients	Wheezing Patients	Controls	AD Patients
Number of patients	27	13	19	70	53	40
Mean age (yr)	0.9	1.2	1.1	7.0	9.9	5.6
Age range	0.3-1.8	0.5-1.8	0.5-1.9	2.0-15.4	2.3-16.1	2.0-13.0
Male (%)	56	27	84	66	64	52
Race: Black (%)	67	45	53	51	33	53
Family history (%)*	56	82	88	83	47	94
Total IgE†	15	4	109	166	27	541
(95% C.I.)	(9-26)	(2-10)	(47-253)	(110-251)	(18-42)	(288-912)
Payment Requirements:‡						
100%	15	58	47	18	31	40
10-75%	11	0	6	26	13	11
0%	73	42	47	56	56	49

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Footnotes for Table 1:

* Analysis of the family history revealed a significantly increased prevalence of asthma, rhinitis, eczema and other allergic symptoms in immediate family members of wheezing and AD patients compared to controls after age 2 ($p < 0.001$ and $p < 0.001$, respectively).

† The total IgE levels in sera are expressed as geometric means in IU/ml. The 95% percent confidence intervals are also expressed in IU/ml.

‡ Payment requirement categories reflect the proportion of the medical bill charged to the patient's family based on annual family income. The percentages of families required to pay 100%, 10-75%, or 0% of their child's bill are shown.

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TABLE 2: Positive RAST Responses to Food and Inhalant Allergens in Wheezing Children*

Sera with IgE ab to one or more:	Age < 2 y (n = 27)		Age 2 - 4 (n = 21)		Age ≥ 4 (n = 49)	
	Positive† Patients (%)	Total‡ IgE	Positive† Patients (%)	Total‡ IgE	Positive† Patients (%)	Total‡ IgE
Food Allergens§	1(4%)	59	5(24%)	140	15(31%)	217
Inhalant allergens‖	2(7%)	102	6(29%)	155	29(59%)	338
Foods only	0(0%)	--	3(14%)	137	5(10%)	55
Inhalants only	1(4%)	178	4(19%)	160	19(39%)	225
Foods and Inhalants¶	2(7%)	102	9(43%)	149	34(69%)	259

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Footnotes for Table 2:

* RAST data for IgE ab to five inhalant allergens (mite, cat, cockroach, ryegrass, and ragweed) were previously reported (18). Sera from 97 wheezing and 55 control patients were available from this study for measurements of IgE ab to food allergens. Sera from an additional 11 control patients were also analyzed.

† Number of RAST positive patients followed by the % who were positive in parentheses.

‡ Total serum IgE levels are reported as geometric means in IU/ml.

§ Sera with IgE ab to food allergens. Some also had IgE ab to inhalants.

‖ Sera with IgE ab to inhalants. Some also had IgE ab to foods.

¶ Total responses to food and inhalant allergens combined

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FIG. 1

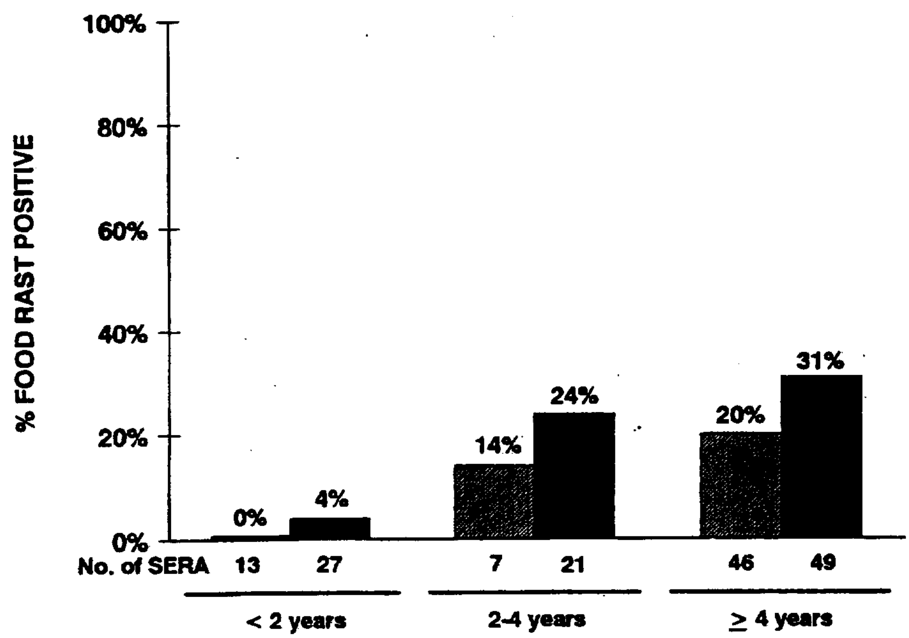

FIG. 2A

A.

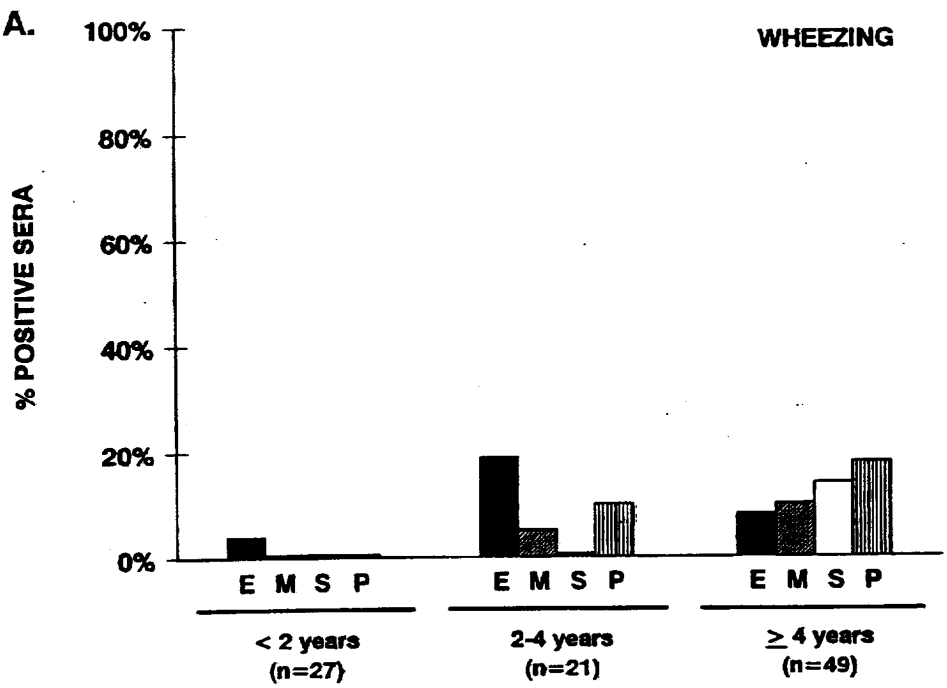

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FIG. 2B

B.

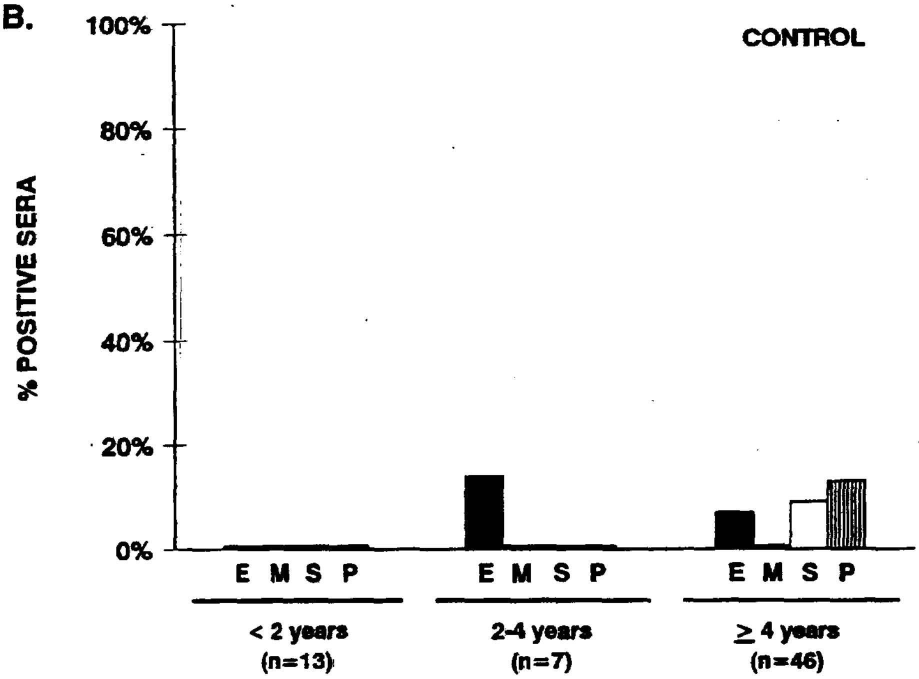

FIG. 2C

C.

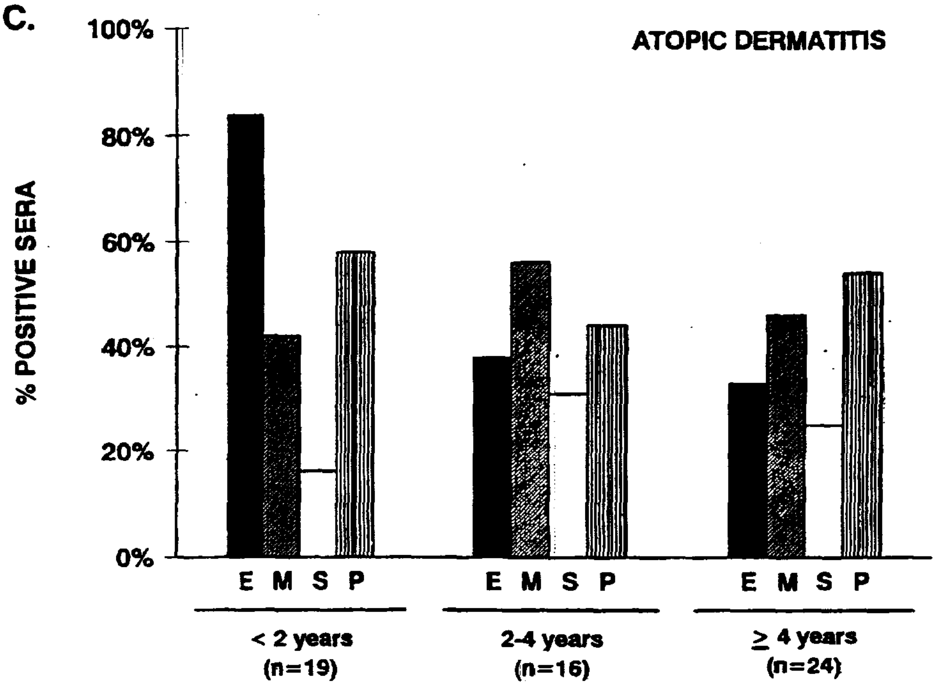

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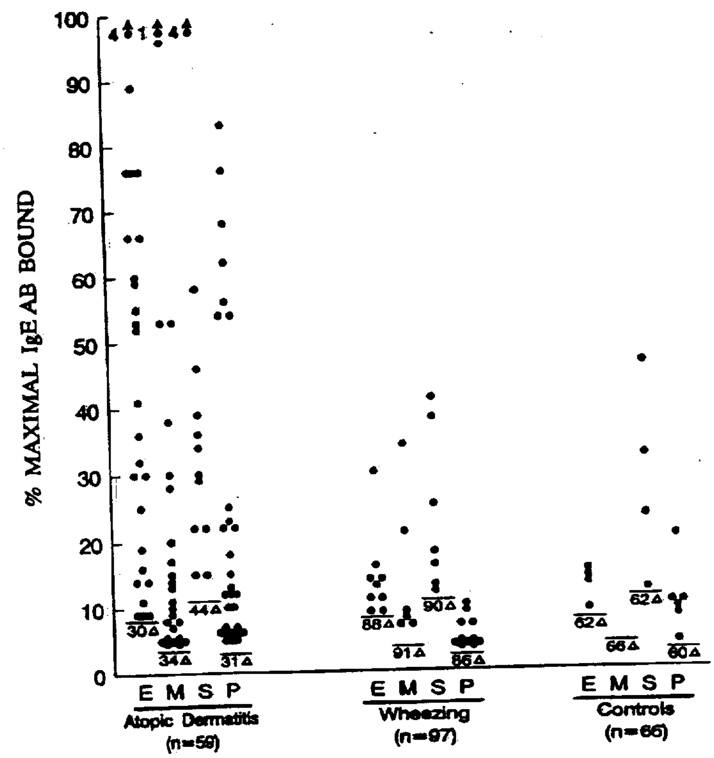
FIG.3



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